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בקשה לפטנט
Application for Patent

C:35181

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(באנגלית) MICROENCAPSULATED AND CONTROLLED-RELEASE FORMULATIONS OF ISOFLAVONE FROM ENRICHED FRACTIONS OF SOY AND OTHER PLANTS
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MICROENCAPSULATED AND CONTROLLED-RELEASE FORMULATIONS OF ISOFLAVONE FROM ENRICHED FRACTIONS OF SOY AND OTHER PLANTS

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C.35181

MICROENCAPSULATED AND CONTROLLED-RELEASE FORMULATIONS OF ISOFLAVONE FROM ENRICHED FRACTIONS OF SOY AND OTHER PLANTS

Field of the Invention

The present invention relates to formulations for the controlled or extended release of certain bioactive compounds, and to processes for the preparation of the same.

Background of the Invention

Isoflavones are compounds found in soy and other plants.

In addition to having estrogenic activity, isoflavones also possess other biological properties including:

* Strong antioxidant activity
* Strong anti cancer activity
* Moderate anti-inflammatory activity

It has been established that isoflavone-enriched fractions or extracts of soy or other plants can serve as important nutritional supplements and therapeutic materials. However, it has been found that many of these fractions or extracts are unstable and that when stored for long periods, the active ingredients are often eliminated or otherwise rendered inactive. In addition, some, if not all, of the isoflavones contained in these fractions or extracts are quickly eliminated from the body.

Summary of the Invention

The present invention seeks to provide improved preparations of isoflavone-enriched fractions which preparations offer a convenient oral dosage form for supplying optimum plasma concentrations of the biologically active compounds contained in the fractions (isoflavones such as Deidzein, Genistein, and Glycitain, as well as other materials) and which facilitates user compliance with recommended procedures.

There is thus provided in accordance with a preferred embodiment of the invention an orally-administrable formulation for the controlled release of an isoflavone-enriched fraction

or mixture of such fractions, said formulation comprising at least one plant fraction enriched in isoflavones and at least one carrier, adjuvant or excipient therefor, said formulation being formulated so as to slowly release the isoflavones contained therein.

There is also provided in accordance with a preferred embodiment of the invention an orally-administrable formulation for the stable storage of an isoflavone-enriched fraction or mixture of such fractions, said formulation comprising at least one plant fraction enriched in isoflavones and at least one carrier, adjuvant or excipient therefor, said formulation being formulated so as to substantially maintain the activity of the isoflavones contained therein for at least six months under storage conditions of standard temperature and pressure.

In the context of the present description and claims, the term "isoflavone-containing fraction" will be understood to refer to an extract or fraction in powdered, granulated or oily form, obtained from soy or other plants, enriched in isoflavones, i.e. containing isoflavones in a higher concentration than is found in an extract from the whole plant. Such fractions may also contain other compounds commonly found in soy or plant fractions or extracts that contain isoflavones, as is known in the art.

In the context of the present description and claims, the term "slowly release" will be understood to mean release the material contained therein into the body over a sustained period, typically about 8-12 hours, although longer periods of time, e.g. 18-24 hours or more, are contemplated within the scope of the invention.

In one preferred embodiment of the invention, the orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction comprises at least one granulated isoflavone-enriched fraction and at least one carrier, adjuvant or excipient therefor, and is characterized in that the total in vitro dissolution time of the formulation required for release of 75% of the active ingredients available from the formulation, is between about 4 and about 18 hours, as determined by the U.S.P. XXIII paddle method at a paddle speed of 150 rpm, using simulated intestinal fluid without the digestive enzymes normally found in intestinal fluid, containing 0.1% w/w sodium dodecyl sulfate (SDS), at pH 6.8, and a temperature of 37°C.

In one preferred embodiment of the invention, the formulation is characterized in that the total amount of granulated isoflavone-enriched fractions contained therein is from about 1 to about 95 wt.%.

In another preferred embodiment of the invention, the formulation is in a form selected from the group consisting of: (i) a matrix tablet, (ii) a multicomponent formulation, (iii) a microcapsule of generally spherical shape, (iv) a microcapsule of generally non-spherical shape, (v) a capsule containing microcapsules, and (vi) a tablet containing microcapsules.

In another preferred embodiment of the invention, the formulation comprises at least one granulated isoflavone-enriched fraction mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes, sugars and sugar alcohols.

In one preferred embodiment of the invention, the formulation is in the form of a tablet comprising at least one granulated isoflavone-enriched fraction embedded in a mixture of polyvinyl chloride an polyvinyl acetate, and magnesium stearate as a lubricant.

In another preferred embodiment of the invention, the formulation is in the form of a tablet comprising at least one granulated isoflavone-enriched fraction embedded in a mixture of polyvinyl chloride and ethylcellulose, magnesium stearate as lubricant, and a material selected from the group of hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose and paraffin.

In a preferred embodiment of the invention, the formulation is in the form of a hard gelatin two-piece capsule filled with microcapsules containing at least one granulated isoflavone-enriched fraction.

In another preferred embodiment of the invention, the formulation is in the form of a tablet comprising microcapsules.

The invention also comprises a process for the preparation of an orally-administ formulation for the controlled release of a granulated isoflavone-enriched fraction or mixtu of such fractions, said formulation comprising at least one granulated isoflavone-enriche fraction and at least one carrier, adjuvant or excipient therefor, said process comprising the steps of:

providing at least one granulated isoflavone-enriched fraction; and

incorporating said at least one granulated isoflavone-enriched fraction into said at least one carrier, adjuvant or excipient therefor;

wherein said formulation is characterized in that the total in vitro dissolution time of said formulation required for release of 75% of the active ingredients from said formulation is between about 4 and about 18 hours, as determined by to the U.S.P. XXIII paddle method, using simulated intestinal fluid without the digestive enzymes normally found in intestinal fluid, containing 0.1% w/w sodium dodecyl sulfate (SDS), at pH 6.8, and a temperature of 37°C.

In one preferred embodiment of the invention, the process is characterized in that the at least one granulated isoflavone-enriched fraction is (i) mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes, sugars and sugar alcohols, and (ii) then compressed into tablets.

In another preferred embodiment of the invention, the process is characterized in that the at least one granulated isoflavone-enriched fraction is (i) mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes and sugars, (ii) then processed into a form selected from the group of microcapsules and pellets, and (iii) the microcapsules or pellets are filled into hard gelatin capsules.

In a preferred embodiment of the invention, the process is characterized in that the at least one granulated isoflavone-enriched fraction is (i) mixed or coated with an adjuvant or

mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes and sugars, (ii) then processed into a form selected from the group of microcapsules and pellets, and (iii) said microcapsules or pellets are compressed into tablets.

There is also provided in accordance with a preferred embodiment of the invention an orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions, comprising particles of at least one granulated isoflavone-enriched fraction coated with a film comprising a mixture of at least one water soluble polymer and at least one water insoluble polymer, the at least one water soluble polymer and the at least one water insoluble polymer being present in a ratio that produces a substantially zero order linear release pattern of at least one active ingredient. In one preferred embodiment of the invention, the particles comprise particles which are non-spherically shaped. In another preferred embodiment of the invention, the particles comprise particles which are spherically shaped.

There is also provided in accordance with a preferred embodiment of the invention an orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions, comprising particles of at least one granulated isoflavone-enriched fraction coated with an enteric coating comprising a polymer film comprising a polymer which is insoluble at a pH below about 5.5. In a preferred embodiment of the invention, the particles comprise particles which are non-spherically shaped. In another preferred embodiment of the invention, the particles comprise particles which are spherically shaped.

In a preferred embodiment of the invention, the polymer is soluble at a pH of about 5.5 or higher. In another preferred embodiment of the invention, the polymer is insoluble at a pH below about 5.0.

In one preferred embodiment of the invention, the polymer is hydroxypropylmethyl cellulose phthalate. In another preferred embodiment of the invention, the polymer is cellulose acetate phthalate.

In a pref nsoluble polymer is ethyl cellulose.

In another preferred embo vater soluble polymer is hydroxypropylmethyl cellulose (HPMC).

In a preferred embodiment of the invention, the water insoluble polymer is ethyl cellulose and the water soluble polymer is hydroxypropylmethyl cellulose (HPMC), and the HPMC/ethyl cellulose ratio is substantially from about 0.05 to about 0.40.

In a preferred embodiment of the invention, the total content of granulated isoflavone-enriched fractions is between about 1 to 95 wt. %.

In accordance with another preferred embodiment of the invention, there is provided a process for producing an orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions, comprising coating particles of granulated isoflavone-enriched fraction or fractions with an inner mixed polymer film comprising ethyl cellulose and hydroxypropylmethyl cellulose (HPMC), wherein the HPMC/ethyl cellulose ratio is substantially from about 0 to about 0.40 by weight, and then coating said particles coated with said inner polymer film with an outer polymer film comprising hydroxypropylmethyl cellulose phthalate, wherein the weight ratio of the outer and inner polymer layers is between about 0.2 to about 5.

Detailed Description of Preferred Embodiments of the Invention

The oral controlled release dosage formulations of granulated isoflavone-enriched fractions, in accordance with the invention, include matrix formulations, such as matrix tablets, and multiparticulate formulations such as microcapsules.

In one preferred formulation of the invention, non-spherically, irregularly shaped isoflavone-enriched fraction granulate particles are coated with a film layer comprising a water insoluble polymer, such as ethyl cellulose, and a water soluble polymer such as

hydroxypropylmethyl ce ... in an HPMC/ethyl cellulose weight ratio s ...

The present inve ... inistrable, controlled-release dosage forms of granulated iso ... one-enriched fractions, especially in either matrix formulations such as matrix tablets or in multiparticulate formulations like microcapsules put into two piece capsules. This is done in order to obtain a delivery system of isoflavone-enriched fraction-derived molecules which will ensure a steady supply of the active components (isoflavones and other active components, if present) for a sustained period. By either embedding the granulated isoflavone-enriched fractions into a matrix formulation or incorporating them into a microcapsule formulation, or both, in order to control or extend the release of the components of the isoflavone-enriched fractions into the surroundings, the following advantages may be obtained in comparison with conventional release formulations:

- A slower in vivo absorption of isoflavone-enriched fraction-derived active molecules, and hence optimal plasma peak values, which thus reduces the occurrence of undesired effects.
- Prolonged and steady plasma concentrations of isoflavone-enriched fraction-derived active molecules over 12 hours which can help avoid underdosing between dosage intervals.
- A significant increase in the relative extent of bioavailability (amount of active ingredient per gram of isoflavone-enriched fraction ingested) of isoflavone-enriched fraction-derived active molecules, i.e. the therapeutically relevant component, in comparison to standard release formulations.
- Higher tolerability of the active ingredients, i.e., fewer side effects.
- Reduction in the number of daily doses required, which together with the higher tolerability can significantly increase user compliance.
- Stabilization of the highly sensitive isoflavone-enriched fraction-derived active ingredients and thus extended shelf life of the end product.
- Provision of an enteric-coated formulation in those products which are sensitive to the low pH of the stomach and ensuring their release only in the intestine.

Coating and matrix materials for obtaining controlled release

Coating and matrix materials which may be used in accordance with the invention are those known in the art for use in controlled-release formulations, such as:

(a) synthetic polymers of the polyvinyl type, e.g. polyvinylchloride, polyvinylacetate and copolymers thereof, polyvinylalcohol, and polyvinylpyrrolidone;

(b) synthetic polymers of the polyethylene type, e.g. polyethylene and polystyrene;

(c) polymers of the acrylic acid or acrylic acid ester type, e.g. methylmethacrylate or copolymers of acrylic monomers;

(d) biopolymers or modified biopolymers, such as cellulose or cellulose derivatives, e.g. ethylcellulose, cellulose acetate phthalate, cellulose acetate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, microcrystalline cellulose, Na-carboxymethyl cellulose, as well as, for example, shellac and gelatin;

(e) fats, oils, higher fatty acids and higher alcohols (i.e. acids and alcohols containing alkyl chains of at least 10 carbon atoms), e.g. aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, 12-hydroxystearl alcohol, glyceryl mono- or dipalmitate, glyceryl mono-, di- or tristearate, myristyl alcohol, stearic acid, stearyl alcohol, and polyethyleneglycols;

(f) waxes, e.g. bees' wax, carnauba wax, Japan wax, paraffin, spermaceti, and synthetic waxes; and

(g) sugars and sugar alcohols, e.g. mannitol, sorbitol, sucrose, xylitol, glucose, and maltose.

Depending on the technique used, the polymers mentioned above can be used as coating agents, matrix adjuvants or pharmaceutical binders. Whether the polymer will function as a matrix adjuvant or a pharmaceutical binder will be dependent on the amount of polymer in the formulation.

Combinations of the above mentioned polymers, fats and waxes can also be used for microencapsulation purposes as well as for matrix formation, viz. different polymers can be mixed, a polymer can be mixed with a fat or wax, and so forth.

The encapsulation of the isoflavone-enriched fraction can be achieved in the form of

microcapsules, but the encapsulation is not restricted to the micro size, i.e. the range of 50 μm to 2000 μm, and can be accomplished on larger particles or granules.

The multiparticulate dosage forms, i.e., microcapsules or coated pellets as well as the matrix tablets useful for the present invention can be prepared by any of several known production processes, including conventional granulation and tableting of matrix tablets, pan coating, prilling, extrusion and spheronization, fluid bed processes, spray drying, spray chilling, coacervation and other processes.

Microcapsules or coated pellets

Microcapsules or coated pellets are defined as a solid or liquid core enclosed in a coating. The coating may also be referred to as the wall or shell. Various types of microcapsule structures can be obtained depending on the manufacturing process, e.g. mononuclear spherical, multinuclear spherical, multinuclear irregular, encapsulated mononuclear capsules, dual-walled microcapsules, etc. Where no distinct coating and core region can be observed, the analogous terms are microparticles, microspheres, micromatrices and microbeads. The microcapsules or pellets of the present invention usually have a particle size between about 1 and about 2000 microns.

The microcapsules or coated pellets of granulated isoflavone-enriched fractions can be filled into empty hard gelatin capsules to an extent corresponding to the desired dose, or they can be gently compressed into a tablet by using suitable tablet excipients.

Coated particles of isoflavone-enriched fraction may also be mixed with a pharmaceutical binder to form micropellets, which are then compressed into tablets.

The orally administrable formulations of the invention may comprise micropellets, which are then coated with a pharmaceutically acceptable coating adjuvant prior to being compressed into tablets. The micropellets can also be filled into capsules.

The formulations of the invention may also comprise microspheres which are then coated with a pharmaceutically acceptable coating adjuvant prior to being filled into

capsules.

Matrix formulations

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipients in order to achieve release by a continuous leaching of the drug from the inert matrix core. The release mechanisms often follows the square root law of Higuchi. This term also applies to a matrix built of hydrophilic substances which in contact with water form a gel of high viscosity.

One type of matrix formulation is a matrix tablet, which is a matrix formulation in tablet form. Such tablets may be coated with an enteric coating, which inhibits or prevents dissolution of the tablets at low pH (below about pH 5, preferably below about pH 5.5), such as is found in the stomach, and enables dissolution of the tablets at higher pH's (e.g. around pH 6.8, such as is found in the intestine).

It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of the features described hereinabove as well as modifications and variations thereof which would occur to a person of skill in the art upon reading the foregoing description and which are not in the prior art.

CLAIMS

1. An orally-administrable formulation for the controlled release of an isoflavone-enriched fraction or mixture of such fractions, said formulation comprising at least one plant fraction enriched in isoflavones and at least one carrier, adjuvant or excipient therefor, said formulation being formulated so as to slowly release the isoflavones contained therein.

2. An orally-administrable formulation for the stable storage of an isoflavone-enriched fraction or mixture of such fractions, said formulation comprising at least one plant fraction enriched in isoflavones and at least one carrier, adjuvant or excipient therefor, said formulation being formulated so as to substantially maintain the activity of the isoflavones contained therein for at least six months under storage conditions of standard temperature and pressure.

3. An orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions according to claim 1, comprising at least one granulated isoflavone-enriched fraction and at least one carrier, adjuvant or excipient therefor, characterized in that the total in vitro dissolution time of said formulation required for release of 75% of the active ingredients available from said formulation is between about 4 and about 18 hours, as determined by the U.S.P. XXIII paddle method at a paddle speed of 150 rpm, using simulated intestinal fluid without the digestive enzymes normally found in intestinal fluid, containing 0.1% w/w sodium dodecyl sulfate (SDS), at pH 6.8, and a temperature of 37°C.

4. A formulation according to Claim 3 characterized in that the total amount of granulated isoflavone-enriched fractions contained therein is from about 1 to about 95 wt.%.

5. A formulation according to Claim 3, wherein said formulation is in a form selected from the group consisting of: (i) a matrix tablet, (ii) a multicomponent formulation, (iii) a microcapsule of generally spherical shape, (iv) a microcapsule of generally non-spherical shape, (v) a capsule containing microcapsules, and (vi) a tablet containing microcapsules.

6. A formulation according to Claim 3 comprising at least one granulated isoflavone-

enriched fraction mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes, sugars and sugar alcohols.

7. A formulation according to Claim 3 in the form of a tablet comprising: at least one granulated isoflavone-enriched fraction embedded in a mixture of polyvinyl chloride and polyvinyl acetate; and magnesium stearate as a lubricant.

8. A formulation according to Claim 3 in the form of a tablet comprising: at least one granulated isoflavone-enriched fraction embedded in a mixture of polyvinyl chloride and ethyl cellulose; magnesium stearate as lubricant; and a material selected from hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose and paraffin.

9. A formulation according to Claim 3 in the form of a hard gelatin two-piece capsule filled with microcapsules containing at least one granulated isoflavone-enriched fraction.

10. A formulation according to Claim 3 in the form of a tablet comprising microcapsules.

11. A process for the preparation of an orally-administrable formulation for the controlled release of granulated isoflavone-enriched fraction or mixture of such fractions, said preparation comprising at least one granulated isoflavone-enriched fraction and at least one carrier, adjuvant or excipient therefor, said process comprising the steps of:

providing at least one granulated isoflavone-enriched fraction, and

incorporating said at least one granulated isoflavone-enriched fraction into said at least one carrier, adjuvant or excipient therefor,

wherein said formulation is characterized in that the total in vitro dissolution of said formulation required for release of 75% of the active ingredients from said formulation based upon the total amount of active ingredients present in said formulation is between about 4 and about 18 hours, as determined by the USP XXIII paddle method at a paddle speed of 150 rpm, using simulated intestinal fluid without the digestive enzymes normally found in intestinal fluid, containing 0.1% w/w sodium dodecyl sulfate (SDS), at pH 6.8 and a

temperature of 37°C.

12. The process according to Claim 11 characterized in that said at least one granulated isoflavone-enriched fraction is (i) mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes, sugars and sugar alcohols, and (ii) then compressed into tablets.

13. The process according to Claim 12 characterized in that said at least one granulated isoflavone-enriched fraction is (i) mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose-type polymers, synthetic polyacrylate-type polymers, fats, waxes and sugars, (ii) then processed into a form selected from the group of microcapsules and pellets, and (iii) said microcapsules or pellets are filled into hard gelatin capsules.

14. The process according to Claim 12 characterized in that said at least one granulated isoflavone-enriched fraction is (i) mixed or coated with an adjuvant or mixture of adjuvants selected from the group consisting of synthetic polyvinyl-type polymers, synthetic polyethylene-type polymers, cellulose type polymers, synthetic polyacrylate-type polymers, fats, waxes and sugars, (ii) then processed into a form selected from the group of microcapsules and pellets, and (iii) said microcapsules or pellets are compressed into tablets.

15. An orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions comprising particles of at least one granulated isoflavone-enriched fraction coated with a film comprising a mixture of at least one water soluble polymer and at least one water insoluble polymer, said at least one water soluble polymer and at least one water insoluble polymer being present in a ratio that produces a substantially zero order linear release pattern of at least one active ingredient.

16. An orally-administrable formulation according to Claim 15, wherein said particles comprise particles which are non-spherically shaped.

17. An orally-administrable formulation according to Claim 15, wherein said particles comprise particles which are spherically shaped.

~~18. An orally-administrable formulation according to claim 15, wherein said at least one~~ active ingredient is Deidzein.

19. An orally-administrable formulation according to claim 15, wherein said at least one active ingredient is Genisein.

20. An orally-administrable formulation according to claim 15, wherein said at least one active ingredient is an Glycitain.

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21. An orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions, comprising particles of at least one granulated isoflavone-enriched fraction coated with an enteric coating comprising a polymer film comprising a polymer which is insoluble at a pH below about 5.5.

22. An orally-administrable formulation according to Claim 21, wherein said particles comprise particles which are non-spherically shaped.

23. An orally-administrable formulation according to Claim 21, wherein said particles comprise particles which are spherically shaped.

24. A formulation according to Claim 21, wherein said polymer is soluble at a pH of about 5.5 or higher.

25. A formulation according to Claim 21, wherein said polymer is insoluble at a pH below about 5.0.

26. A formulation according to Claim 21, wherein said polymer is hydroxypropylmethyl cellulose phthalate.

27. A formulation according to Claim 21, wherein said polymer is cellulose acetate phthalate.

28. A formulation according to Claim 15 wherein said water insoluble polymer is ethyl cellulose.

29. A formulation according to Claim 15 wherein said water soluble polymer is hydroxypropylmethyl cellulose (HPMC).

30. A formulation according to Claim 15 wherein said water insoluble polymer is ethyl cellulose and said water soluble polymer is hydroxypropylmethyl cellulose (HPMC), and wherein the HPMC/ethyl cellulose ratio is substantially from about 0.05 to about 0.40.

31. A formulation according to Claim 15 wherein the total content of granulated isoflavone-enriched fractions is between about 1 to 95 wt. %.

32. A process for producing an orally-administrable formulation for the controlled release of a granulated isoflavone-enriched fraction or mixture of such fractions, comprising coating particles of at least one granulated isoflavone-enriched fraction with an inner, mixed polymer film comprising ethyl cellulose and hydroxypropylmethyl cellulose (HPMC), wherein the HPMC/ethyl cellulose ration is substantially from about 0 to about 0.40 by weight, and then coating said particles coated with said inner polymer film with an outer polymer film comprising hydroxypropylmethyl cellulose phthalate, wherein the weight ratio of the outer to inner polymer layers is between 0.2 to 3.0.

For the Applicant,

Sanford T. Colb & Co.
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